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Cancer Mortality in a Radiation-exposed Cohort of Massachusetts Tuberculosis Patients

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ABSTRACT

The mortality experience of 13,385 tuberculosis patients treated between 1925 and 1954 in Massachusetts was determined through August 1986. Among 6,285 patients examined by X-ray fluoroscopy an average of 77 times during lung collapse therapy and followed for up to 50 yr (average = 25 yr), no increase in the total number of cancer deaths occurred [standardized mortality ratio (SMR) = 1.05, *n* = 424]. In contrast, the 7,100 patients treated by other means were at significant risk of dying from cancer (SMR = 1.3), especially of sites linked to cigarette smoking and alcohol use. Among the irradiated patients, estimates of mean radiation doses to the breast, lung, esophagus, and active bone marrow were 0.75, 0.84, 0.80, and 0.09 Gy, respectively. Cancers of the breast (SMR = 1.4, *n* = 62) and esophagus (SMR = 2.1, *n* = 14) were significantly increased. The risk of esophageal cancer, however, decreased with time since exposure. Lung cancer (SMR = 0.8, *n* = 69) and leukemia (SMR = 1.2, *n* = 17) were not elevated. Despite a wide range of doses to the lung, reaching over 8 Gy, there was no evidence of a dose response. Lung cancer risk also did not vary by time since exposure or age at exposure. Adjustment for smoking and the amount of lung tissue at risk did not appreciably modify these findings. These data suggest that frequent exposures to low doses of radiation over a period of several years increase the occurrence of cancer of the breast. When compared with studies of atomic bomb survivors, however, the fractionated exposures experienced by this cohort appear less effective in causing lung cancer than single exposures of the same total dose.

INTRODUCTION

Although it has been demonstrated that the risk of lung cancer is increased after exposure to X-rays or γ-rays (1, 2), there is uncertainty as to the magnitude of the risk following low-dose exposures received over a period of many years. A slight excess of lung cancer was observed among pioneering British radiologists (3) for whom the occupational exposures were likely to have been excessive, but no risk was evident among similar professionals practicing in the United States (4) or in China (5). Several studies of workers in the nuclear industry have failed to find an increase in lung cancer (6–10), but the low doses received made it unlikely that a radiation effect could be detected. TB[2] patients given multiple chest fluoroscopies during pneumothorax therapy have been recommended as a valuable group to study for subsequent lung cancer (11) because the exposure to the lung was large, patients could be followed for long periods of time after treatment, and other patients were available for comparison who received treatment for TB by means that did not include fluoroscopic monitoring. In this paper we report results from an extended follow-up of two series of TB patients (12, 13) and combine the findings with a previously unevaluated group of 4,718 subjects. Overall, 13,385 patients treated for TB in Massachusetts between 1925 and 1954 have now been studied.

SUBJECTS AND METHODS

Patients diagnosed with pulmonary TB between 1925 and 1954 and discharged alive from 12 Massachusetts hospitals were identified, and their medical records were abstracted (Table 1). Data on the pneumothorax treatments, fluoroscopic X-ray exposures, and relevant factors, such as smoking and alcohol use, were obtained. Information to assist in locating study subjects was also abstracted from the medical records as described previously (14).

The initial cohort (TB-I) included primarily young women of whom 60% received air collapse therapy at an average age of 24 yr (Table 1). This group received on average more pneumothorax treatments (*n* = 101) and associated radiation exposure than the other two cohorts. The second cohort (TB-II) included older female and all male patients from the same institutions as the initial cohort. Female patients of all ages were also identified from several additional tuberculosis sanatoria. The average age of first exposure was 9 yr higher in TB-II than in TB-I. The average number of examinations was fewer (*n* = 80), and resulted in a lower range of radiation doses to organs of interest. The third cohort (TB-III) incorporated the remaining male patients treated at institutions from the second study and included all subjects from several new institutions. The TB-III group was composed primarily of males, and the subjects received fewer fluoroscopic examinations (mean = 57), were first exposed at later ages (mean age = 38 yr), and had fewer years of follow-up (mean = 19 yr) than the earlier cohorts.

Exposure groups were defined by air collapse therapy (pneumothorax and pneumoperitoneum) treatment records. Air collapse therapy was standard treatment for TB in the 1930s and 1940s and involved air being injected into the pleural cavity to force lung tissue away from the chest wall. Typically this procedure was repeated, with the aid of a fluoroscopic examination, 2 to 3 times per month for over 2 yr, and up to 5 yr for patients with advanced disease. In the three cohorts combined, 47% (6285) were exposed to air collapse therapy involving an average of 77 examinations performed over an average of 29 mo. This larger sample size and broad range of exposures allowed a more precise evaluation of radiation dose effects by age of exposure and time since exposure than was previously possible.

Estimates of the radiation dose absorbed in several organs adjacent to the lung and exposed during the fluoroscopic procedures were made using a previously described dosimetry model (15, 16). This methodology took into account the number of fluoroscopies, calendar year of exposure, age at treatment, and machine exposure parameters to the extent possible. The first reported breast doses (15) were based on somewhat different assumptions than those computed later for other organs (16) and, subsequently, also for the breast (17). The present work uses the later calculations (16). Based upon interviews with both the physicians who conducted the examinations and the patients themselves, the average fluoroscopy time was estimated to have lasted 15 s, and the patients were estimated, on average, to have faced the X-ray tube 25% of the time (15). Variation in rotation would have a minimal effect on site-specific dose estimates, with the exception of breast doses.

Follow-up of all three study groups to determine vital status has been carried out concurrently to August 31, 1986. Deaths were ascertained by searching records of Vital Statistics Offices in the state of last known residence, by computer linkage with mortality files of the Social Secu-

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[2] The abbreviations used are: TB, tuberculosis; CI, confidence interval; SMR, standardized mortality ratio, number of observed cases divided by number expected; CRR, crude rate ratio, rate in exposed divided by the rate in the unexposed; PY, person-years; Gy, gray, unit of absorbed dose: 1 Gy = 100 rad; 10 mGy = 1 rad.

Table 1 *Description of three Massachusetts cohorts of tuberculosis patients*

Description of cohort	TB-I (16) [a]	TB-II (13)	TB-III	Combined
Yr cohort identified	1972–1975	1978–1980	1979–1982	1972-1982
No. of hospitals	2	8 [b]	9 [c]	12
No. of subjects	1,741	6,926	4,718	13,385
Median yr of birth	1,917	1,911	1,905	1,910
Yr of birth (range)	1876–1942	1849–1945	1852–1941	1849–1945
% female	100	39	12	49
% deceased	38	53	71	58
% exposed	60	49	40	47
Mean yr of follow-up	34	27	19	25
Mean age at first exposure (yr)	24	33	38	33
Mean no. of fluoroscopies	101	80	57	77
Mean duration of exposure (mo)	32	29	26	29
Estimated mean dose (Gy)				
Lung	1.12	0.86	0.61	0.84
Esophagus	1.06	0.83	0.59	0.80
Breast	0.96	0.65	0.54	0.75
Trunk	0.33	0.25	0.18	0.25
Active bone marrow [d]	0.12	0.10	0.07	0.09
Pancreas	0.08	0.06	0.05	0.06
Stomach	0.08	0.06	0.04	0.06

[a] Numbers in parentheses, reference number.
[b] Two overlap with TB-I.
[c] Five overlap with TB-II.
[d] Averaged over total body.

rity Administration and the National Death Index, and by contacting relatives and friends. Vital status was also confirmed through the post office, motor vehicle departments, credit bureaus, and other sources as previously described (14). For those who died, death certificates were obtained, and all causes of death were reviewed and coded using the eighth revision of the International Classification of Diseases (18). Overall, 58% (7735) of the subjects had died, 35% (4636) were found to be alive, and 7.6% (1014) were lost at the end of the follow-up period. The proportion of losses was similar between exposed and unexposed groups for both sexes, although women were less likely to be located than men overall (Table 2).

A mail survey was conducted throughout the study period to obtain additional information on known cancer risk factors, including smoking and alcohol histories. Information was also compiled from medical records and combined with questionnaire responses to categorize ever, never, or unknown use for smoking and alcohol (Table 2). Smoking and alcohol histories could be reconstructed for 70% and 65% of the patients, respectively.

The duration of follow-up was defined from the date of index hospitalization discharge to the date last known to be alive or the date of death. The average length of follow-up was 25 yr. The 13,385 subjects in this study do not include the 335 with no follow-up information

Table 2 *Description of Massachusetts cohorts combined by gender and exposure status*

	Females				Males			
	Exposed		Unexposed		Exposed		Unexposed	
	No.	%	No.	%	No.	%	No.	%
Vital Status [a]								
Alive	1569	47	1493	47	849	29	725	19
Dead	1441	43	1363	43	1927	65	3004	77
Lost to follow-up	319	10	328	10	180	6	187	5
Yr since index hospitalization								
<2	302	9	374	12	337	11	744	19
2–4	220	7	173	5	307	10	467	12
5–9	183	6	205	6	313	11	526	13
10 or more	2624	79	2432	76	1999	68	2179	56
Stage of TB								
Minimal	519	16	964	30	299	10	813	21
Moderate	1499	45	1002	32	1257	43	1420	36
Advanced	1283	39	672	21	1379	47	1549	40
Other	22	1	511	16	19	1	132	3
Unknown	6	0	35	1	2	0	2	0
Lung surgery [b]								
Yes	926	28	363	11	795	27	431	11
None recorded	2403	72	2821	89	2161	73	3485	89
Smoking history								
Never	1345	40	1229	39	331	11	339	9
Ever	1067	32	808	25	1884	64	2393	61
Unknown	917	28	1147	36	741	25	1184	30
Alcohol use								
Never	695	21	757	24	623	21	849	22
Sometimes	1496	45	1427	45	1281	43	1536	39
Unknown	1138	34	1000	31	1052	36	1531	39
Total	3329	100	3184	100	2956	100	3916	100

[a] Lost were assumed alive at time of loss.
[b] Pneumonectomy, lobectomy, or thoracoplasty.

since the date of first discharge. One subject included in a previous report (12) was excluded when a corrected date of discharge placed her in an exclusion category. Time since first exposure was taken as the date of first air collapse therapy examination. When this date was not available, the date of first diagnosis of TB or admission was used, in that order. Age at first exposure was estimated in a similar fashion.

Age and calendar time standardized numbers of expected deaths were calculated for each exposure group by sex using US population death rates from 1925 to 1980 and compared with the observed deaths in the group as SMRs (19). SMRs combining males and females are reported throughout this paper. Crude relative risks comparing the annual mortality rate in the exposed to the rate in the unexposed were estimated for leukemia and lymphoma subtypes, because population mortality rates over the time interval under study were not available for the specific classifications desired. Confidence intervals were calculated using exact methods (20). Testing for linear trend of increasing SMR with increasing time since exposure was done by applying the multiplicative model of Breslow *et al.* (21).

Age at exposure and dose level comparisons were restricted to individuals who had survived a specified number of years after their index hospitalization (Table 2). A 10-yr interval was selected for lung and breast cancer, a 2-yr interval was selected for leukemia and lymphoma, and a 5-yr interval was selected for esophageal cancer. These intervals were chosen to be consistent, in large part, with current understanding of minimum appearance times for radiation-induced cancers (22, 23).

RESULTS

The overall mortality experience according to gender and exposure status was remarkably similar (SMRs between 1.7 and 2.0; Table 3). As anticipated, tuberculosis was the primary cause of death, accounting for 40% of the 7735 deaths (SMRs between 62 and 77). Another 8% of all deaths were due to nonmalignant respiratory disease (SMRs between 2.3 and 3.2). Except among nonexposed males, no other significant elevation in death for other nonmalignant disease categories was observed. Significant excesses among nonexposed males were seen for practically all major cause-of-death groups, including cancer (SMR = 1.5), circulatory disorders (SMR = 1.1), and cirrhosis of the liver (SMR = 1.6).

Radiation exposure was not associated with an overall increase in cancer mortality among females or males. Three individual cancer sites were increased significantly among exposed patients: breast cancer among women (SMR = 1.4), and cancers of the mouth (SMR = 2.2) and bone (SMR = 4.2) among men. Two cancer sites were significantly below expectation: cancer of the stomach (SMR = 0.3) and lung (SMR = 0.8) among men.

Aggregating males and females revealed an excess of esophageal cancer among the exposed (SMR = 2.1, 95% CI = 1.2–3.6). In contrast, no overall excesses were apparent for lung cancer (SMR = 0.8, 95% CI = 0.6–1.0) or leukemia (SMR = 1.2, 95% CI = 0.7–1.9). In the 2- to 10-yr period after first exposure where the appearance of any radiation-induced leukemias would have been most likely, only 2 cases of leukemia were observed compared with 1.4 expected.

Relative risks comparing rates in the exposed to the unexposed groups for certain types of leukemia and lymphoma are shown in Table 4. No case of chronic lymphatic leukemia occurred among exposed subjects, and radiation did not appear to increase the risk of non-chronic lymphatic leukemia (CRR = 0.9). Multiple myeloma and non-Hodgkin's lymphoma also were not elevated in the exposed group, although few cases were observed.

Cancer sites of particular interest were evaluated by time since first exposure (Table 5). Lung cancer was significantly decreased among 10-yr survivors (SMR = 0.7, 95% CI = 0.6–

Table 3 *No. of deaths observed and SMRs among tuberculosis patients by gender and exposure group*

		Females				Males			
		Exposed		Unexposed		Exposed		Unexposed	
Cause of death	ICDA8 [a]	OBS	SMR	OBS	SMR	OBS	SMR	OBS	SMR
All deaths		1,441	2.0 [b]	1,363	1.7 [b]	1,927	1.9 [b]	3,004	2.0 [b]
Tuberculosis	010–019	646	77.4 [b]	468	61.9 [b]	858	67.3 [b]	1,115	64.8 [b]
All cancer	140–209	221	1.1	208	1.0	203	1.0	412	1.5 [b]
Buccal	140–149	1	0.4	5	1.9	14	2.2 [b]	29	3.3 [b]
Esophagus	150	4	2.3	1	0.6	10	2.1	17	2.5 [b]
Stomach	151	10	1.5	9	1.1	3	0.3 [b]	30	1.4
Large intestine	153	21	1.0	28	1.2	25	1.3	46	1.7 [b]
Rectum	154	10	2.0	9	1.6	11	1.7	14	1.3
Liver	155, 156	3	0.6	2	0.3	1	0.2	7	1.0
Pancreas	157	10	1.1	5	0.5	8	0.7	17	1.1
Larynx	161	0	0.0	1	1.9	3	1.0	15	3.6 [b]
Lung	162	19	0.8	22	1.0	50	0.8 [b]	104	1.4 [b]
Bone	170	1	1.3	0	0.0	4	4.2 [b]	3	2.0
Skin	172, 173	2	0.8	5	2.0	3	0.9	7	1.6
Breast	174	62	1.4 [b]	47	1.1				
Cervix uteri	180	14	1.6	16	1.9 [b]				
Bladder	188	2	0.8	1	0.4	12	1.9	20	1.9 [b]
Kidney	189	2	0.7	1	0.3	8	1.6	10	1.6
Brain	191, 192	2	0.4	7	1.5	5	0.9	9	1.6
Thyroid	193	1	1.5	1	1.4	1	2.6	0	0.0
Hodgkins disease	201	5	3.1	2	1.3	2	0.9	3	1.2
Leukemia	204–207	9	1.4	7	1.1	8	1.0	14	1.3
Non-Hodgkin's [c]		6	0.7	6	0.7	7	0.8	8	0.8
Other cancers		37	0.8	33	0.8	28	0.8	59	1.2
Benign neoplasms	210–239	3	0.8	2	0.5	1	0.4	9	2.7
Respiratory	460–519	111	3.2 [b]	88	2.3 [b]	153	2.4 [b]	272	2.9 [b]
Circulation	390–458	309	1.0	440	1.1	517	1.0	925	1.1 [b]
Cirrhosis of liver	571	17	1.2	14	1.1	29	1.3	40	1.6 [b]
Other deaths		134	1.0	143	1.0	166	0.9	231	0.9
No. of subjects		3,329		3,184		2,956		3,916	
Total person-years		100,057		92,588		69,368		68,993	

[a] ICDA8, eighth revision of the International Classification of Diseases. OBS, number of deaths observed.
[b] $P <= 0.05$, two-sided test.
[c] Includes ICDA codes 200, 202, 203, and 208.

Table 4 *No. of deaths, crude relative risks and 95% confidence intervals for selected lymphopoietic cancer sites in 2-yr survivors*

Cause of death	ICDA8 [a]	No. of deaths: Exposed	No. of deaths: Unexposed	Crude relative risk	95% CI
Leukemia					
Non-CLL	204–207 [b]	17	17	0.9	0.5–1.8
CLL	204.1	0	3	0.0	0.0–1.3
Multiple myeloma	203	2	5	0.4	0.1–1.8
Non-Hodgkin's lymphoma	200, 202	10	7	1.3	0.5–3.5
Person-years		157,578	148,794		

[a] ICDA8, eighth revision of the International Classification of Diseases, CLL, chronic lymphatic leukemia.
[b] Excludes 204.1.

Table 5 *Cancer deaths for selected sites among exposed subjects by time since first exposure*

Cause of death	Time since first exposure (yr): 0–9	10–19	20–29	30–39	40+	Total
Lung						
Observed	6	5	13	25	20	69
Expected	3.5	8.6	19.6	32.6	25.2	89.5
SMR	1.7	0.6	0.7	0.8	0.8	0.8 [a]
Esophagus						
Observed	3	3	2	4	2	14
Expected	0.4	0.8	1.5	2.3	1.7	6.7
SMR	7.5	3.8	1.3	1.7	1.2	2.1 [a]
Leukemia						
Observed	2	3	4	2	6	17
Expected	1.4	2.2	3.2	4.2	2.8	14.4
SMR	1.4	1.4	0.9	0.5	1.9	1.2
No. starting interval	6,285	4,623	4,025	3,388	1,825	6,285
Person-years	44,169	43,860	38,229	29,385	13,783	169,425
Breast [b]						
Observed	2	8	24	18	10	62
Expected	2.6	6.7	11.9	14.4	9.1	44.7
SMR	0.8	1.2	2.0	1.3	1.1	1.4 [a]
No. starting interval	3,329	2,624	2,401	2,103	1,177	3,329
Person-years	24,138	25,414	23,073	18,448	8,984	100,057

[a] $P <= 0.05$, two-sided test.
[b] Female only.

0.9), and the risk for esophageal cancer decreased with time since exposure. Among women followed for over 10 yr, a 43% excess mortality due to breast cancer was apparent (SMR = 1.4, 95% CI = 1.1–1.8).

Lung Cancer Mortality. The absence of an increase in lung cancer mortality was consistent across age at exposure and dose categories (Table 6). To the extent possible, lung cancer risk was examined in light of data on smoking, the major cause of this disease. Factors with some potential to obscure an association, such as stage of TB and lung surgery, were also evaluated. Specifically, patients with more advanced TB would have greater amounts of lung tissue destroyed by the necrotizing processes of the disease itself. Surgery would also result in a smaller volume of lung tissue remaining at risk of developing a later malignancy.

Table 6 *Lung cancer mortality in 10-yr survivors by age at exposure and dose level*

Eight cancers from 326 subjects with unknown dose have been excluded.

Age at exposure (yr)	Dose (Gy absorbed in lung tissue): None	<0.5	0.5–0.99	>=1.0
Under 30				
Observed	23	12	3	10
Expected	31.6	16.3	10.0	18.8
SMR	0.7	0.7	0.3	0.5
Mean dose	0.0	0.20	0.72	1.98
Person-years	67,861	28,702	17,456	34,344
30 and over				
Observed	60	17	6	7
Expected	50.6	19.3	5.1	9.1
SMR	1.2	0.9	1.2	0.8
Mean dose	0.0	0.17	0.70	1.79
Person-years	39,233	16,266	4,737	8,702
All ages				
Subjects	4,611	1,881	854	1,562

Subjects with a record of lung surgery were about half as likely to die of lung cancer, irrespective of whether pneumothorax was performed (Table 7). Among exposed subjects with no record of lung cancer surgery, the risk of lung cancer was still below expectation, although the deficit was no longer statistically significant (SMR = 0.8, 95% CI = 0.6–1. 1). To minimize the obvious problem of evaluating lung cancer risks among subjects whose surgical procedure removed substantial segments of the tissue at risk, the effects of smoking and stage of disease were analyzed only among those with no history of lung surgery. Advanced TB, however, did not seem to lower the risk of lung cancer in patients with no recorded lung surgery (Table 7).

The pattern of smoking history was similar among exposed and unexposed subjects, although the proportion of males who ever smoked (over 60%) was much larger than the proportion of females (over 25%) (Table 2). Analysis restricted to subjects with no record of lung surgery did not shown an association between radiation exposure and subsequent development of lung cancer in either smokers or nonsmokers (Table 7). As anticipated, a deficit of lung cancer deaths was observed in never smokers, among both exposed and unexposed groups, when comparisons were made with rates from the general population which includes both smokers and nonsmokers. An excess of lung cancer was only evident among unexposed subjects with unknown smoking histories.

Esophageal Cancer Mortality. An excess of esophageal cancer was suggested among 5-yr survivors who received an estimated 0.5 Gy or more of absorbed dose to the esophageal tissue (Table 8). A dose-response relationship, however, was not apparent

Table 7 *Lung cancer mortality in 10-yr survivors for selected variables by exposure group*

Variable	Exposed			Unexposed		
	OBS [a]	SMR	95% CI	OBS	SMR	95% CI
Any lung surgery						
None recorded	50	0.8	0.6–1.1	77	1.1	0.9–1.3
Yes	13	0.5	0.3–0.9	6	0.5	0.2–1.2
Stage of TB [b, c]						
Minimal	4	0.4	0.1–1.0	40	1.3	0.9–1.8
Moderate/advanced	46	0.9	0.7–1.2	37	0.9	0.7–1.3
Smoking history [b, d]						
Never	6	0.4	0.2–0.9	4	0.3	0.1–0.7
Ever	33	0.9	0.6–1.3	37	1.0	0.7–1.3
Unknown	11	1.0	0.5–1.8	36	1.9	1.4–2.7

[a] OBS, observed.
[b] Subjects with lung surgery excluded.
[c] Subjects with other and unknown stages excluded.
[d] Including the subjects who had received lung surgery, this variable did not change appreciably any of the SMRs.

Table 8 *Esophagus cancer mortality in 5-yr survivors by age at exposure and dose level*

One cancer from 360 subjects with unknown dose has been excluded.

Age at exposure (yr)	Dose (Gy absorbed in esophageal tissue) [a]			
	None	<0.5	0.5–0.99	>=1.0
Under 30				
Observed	1	0	1	3
Expected	2.1	1.1	0.7	1.2
SMR	0.5	0.0	1.5	2.5
Mean dose	0.0	0.21	0.73	1.93
Person-years	79,694	35,389	20,917	38,687
30 or over				
Observed	9	2	3	1
Expected	5.3	1.8	0.5	0.7
SMR	1.7	1.1	6.6	1.4
Mean dose	0.0	0.16	0.73	1.76
Person-years	52,193	21,118	6,367	10,140
All ages				
Subjects	5,342	2,188	963	1,608

[a] Overall trend $P = 0.25$, one-sided.

Table 9 *Breast cancer mortality in 10-yr survivors by age at exposure and dose level*

Three cancers from 163 subjects with unknown dose have been excluded.

Age at exposure (yr)	Dose (Gy absorbed in breast tissue) [a]			
	None	<0.5	0.5–0.99	>=1.0
Under 30				
Observed	33	12	11	19
Expected	20.9	10.6	5.9	9.6
SMR	1.6 [b]	1.1	1.9	2.0 [b]
Mean dose	0.0	0.21	0.75	1.83
Person-years	46,939	20,880	12,043	18,988
30 or over				
Observed	9	6	2	7
Expected	16.1	7.2	2.3	3.1
SMR	0.6	0.8	0.9	2.3
Mean dose	0.0	0.16	0.74	1.65
Person-years	19,006	8,970	2,975	10,140
All ages				
Subjects	2,432	1,161	529	771

[a] Overall trend $P = 0.01$, one-sided.
[b] $P < 0.05$.

(trend $P = 0.25$). Unfortunately, the possible confounding effect of cigarette smoking and alcohol use could not be adequately evaluated (Table 2). Among the exposed subjects surviving 5 or more yr, all cases of esophageal cancer occurred among smokers, and alcohol use was linked to an elevated risk (SMR = 2.3, 95% CI = 0.5–5.0). No risk of esophageal cancer due to alcohol consumption was apparent among the unexposed (SMR = 0.8 with 95% CI = 0.1–2.8).

Breast Cancer. Breast cancer mortality was increased significantly among women who received 1.0 Gy or more of absorbed dose to the breast tissue (Table 9). For all ages combined, a dose response was suggested (trend $P = 0.01$). Among the unexposed, a peculiar excess of breast cancer was observed among those diagnosed with TB when under age 30, and a peculiar deficit was seen for those diagnosed with TB after age 30.

DISCUSSION

A follow-up study of 13,385 patients with pulmonary TB did not identify an overall increase in cancer deaths among subjects who received an average of 77 chest fluoroscopies over a period of several years. The determination of vital status was very complete, over 90%, and the period of observation was up to 50 yr (mean = 25 yr). The findings indicate that the carcinogenic effect of multiple low-dose X-ray exposure is not likely to be greater than currently assumed (22, 23) and may very well be less for many sites, most notably the lung.

Among the 6,285 patients repeatedly exposed to chest fluoroscopies, a 20% deficit in deaths due to lung cancer was observed in comparison to the general population. There was no evidence of a dose response, despite lung doses up to 8 Gy, and risk did not vary by time since exposure. A low risk might have been expected because surgical procedures to treat TB would have removed lung tissue from being at risk for cancer development. The influence of surgery as well as the extent of TB on lung cancer risk was evaluated, but these factors could only partially account for the observed deficit. Further, the deficit in males was even greater when the nonexposed TB patients were used for comparison. It is also possible that the diagnosis of TB or the prolonged use of air collapse therapy resulted in differential cessation of smoking, factors which could contribute to a deficit. Although the data were limited, a radiation effect was still not apparent when allowance for smoking history was made. In contrast, excess lung cancer deaths have been reported among survivors of the atomic bombs in Japan (1) and among British patients given radiotherapy for spondylitis (2). Given the relatively high lung dose (mean = 0.84 Gy) in our series, the long period of observation, and the large number of lung cancers, our findings do not seem consistent with these previous studies. This implies, perhaps, that multiple fractionated radiation exposures to the lung are not as effective in causing cancer as a single dose (or several doses) of the same magnitude. A similar reduction in cancer risk is also seen in experimental studies when dose is spread over time (24).

The possible association between pulmonary TB and lung cancer has been intensely studied for several decades. Most recently, a large case-control study in Shanghai concluded that TB may predispose to lung cancer, especially among recent survivors of the disease (25). A large cohort series of TB patients in Canada also reported an elevated relative risk of 1.5 for subsequent lung cancer (26). Overall, no increase was found in our study (SMR = 1.07; 95% CI = 0.9–1.2; n = 195), and we have no explanation for these apparent discrepancies. Interestingly, isoniazid, a drug commonly used to treat TB infection, does not appear related to human lung cancers (26, 27).

Similar to incidence (12, 17, 28, 29) and mortality (30) surveys of irradiated populations, breast cancer deaths were significantly elevated among TB patients who received an average breast dose of 0.75 Gy. The breast appears to be one of the most sensitive organs to the carcinogenic effect of radiation, and fractionation of the dose over time does not appear to diminish risk. Further, linearity of the dose response generally has been characteristic of radiogenic breast cancer, and young women appear at highest risk. Our results add little to these previous observations, although the consistency of our data with these other surveys adds to the importance of our negative finding for radiogenic lung cancer and leukemia. The absence of a lung cancer risk in the presence of a breast cancer risk also resembles the results from a recent study of medical diagnostic X-ray workers in China (5). Interestingly, in experimental studies of mice, the carcinogenic response to fractionated exposures appears to depend on both the dose per fraction and the tissue irradiated (31). For the female BALB/c mouse, significant excess cancers are observed at much lower doses for the breast than for the lung. Further, for the same total dose, low-dose fractions of about 0.05 Gy per fraction produce the same tumor yield for breast cancer as acute single exposures, whereas even 1 Gy per fraction result in a lower yield for lung cancer. (For comparison, the doses per fraction in our series were approximately 0.01 Gy for both the breast and the lung.) The laboratory data imply that the breast may be more susceptible to the carcinogenic effect of radiation than the lung, and also that lower dose fractions are more effective in inducing breast cancer than lung cancer.

We attempted to evaluate whether a protective effect associated with many fractionated exposures could be discerned within the current series, holding dose to the breast or lung constant. Unfortunately, the number of fluoroscopies was so highly correlated with organ doses of individuals that this question could not be adequately addressed.

Cancer of the esophagus is increased among Japanese atomic bomb survivors (1) and British spondylitic patients given radiotherapy (2). It is conceivable that radiation contributed somewhat to the excess seen in our study. However, the number of cancers is small, risk was elevated among the nonexposed males, risk declined with time since exposure, other esophageal cancer risk factors could not be adequately addressed, and the evidence for a dose response was weak. The lack of a lung cancer excess argues against the elevation of esophageal cancer risk being due to smoking, a common risk factor for both sites. However, all 5-yr survivors who received pneumothorax treatments and developed cancer of the esophagus also had a history of smoking cigarettes. While a radiation effect cannot be completely ruled out, other factors such as increased alcohol consumption must be considered as possible contributors to the small excess observed.

Leukemia was not significantly increased following excessive exposure to chest fluoroscopies. The machines used to conduct these fluoroscopic examinations of the lung resulted in high exposures to the skin, approximately 400 to 800 roentgens for our population (15). However, computing the dose to the active bone marrow, averaged over the entire body, resulted in an estimated dose of only 0.09 Gy. This very low dose would not be expected to result in a significant elevation of leukemia. Because the confidence interval about the SMR of 1.2 is wide, the results are not inconsistent, in a statistical sense, with other more powerful studies of populations exposed to higher doses. On the other hand, these findings do not support risk estimates for radiogenic leukemia that are a magnitude higher than currently accepted (22, 23).

Multiple myeloma is elevated among atomic bomb survivors (1) and among several other populations (32), including American radiologists (4). In contrast, large series of patients treated with radiation for cervical cancer (33) and Chinese medical radiation workers (5) have failed to identify increased risks. The very low risk observed in our series also does not support a radiation association and is consistent with conclusions reached by the NIH committed that developed radioepidemiological tables (23).

On the basis of our mortality and dosimetry data, radiation risk coefficients can be crudely estimated for several sites. For the breast, the excess relative risk per Gy is 57%, and the excess absolute risk is 3.14 per 10,000 women per year per Gy for 10-yr survivors. Estimates for breast cancer mortality among atomic bomb survivors are 63% per Gy and 1.2 per 10,000 PY per Gy (34); among Canadian women with TB given fluoroscopy, the estimates are approximately 53% per Gy and 2.59 per 10,000 PY per Gy (35). Similar estimates for esophageal cancer in our series are 95% and 0.47 per 10,000 PY per Gy for 5-yr survivors, but once again the absence of a clear dose response, the decline in risk over time, and the possible influence of confounding factors necessitate caution in interpretation. Among atomic bomb survivors, these estimates are 58% per Gy and 0.45 excess deaths per 10^4 PY per Gy for esophageal cancer (34). For leukemia, nonsignificant estimates are 200% per Gy and 2.3 per 10,000 PY per Gy for 2-yr survivors; however, these coefficients are based on small numbers and are quite unstable.

Among 10-yr survivors of TB, a significant deficit of lung cancer was observed (SMR = 0.7; 95% CI = 0.56–0.94) despite an average dose of 0.84 Gy. Applying the radiation risk coefficients for lung cancer mortality from the study of atomic bomb survivors (63% per Gy and 1.68 per 10^4 PY per Gy) to our series results in a prediction that 24 radiation-induced lung cancers should have occurred over the entire follow-up interval and 18 among 10-yr surivors. Among 10-yr survivors, 63 lung cancer deaths were actually observed, 86 were expected based upon national death rates alone, and 104 would have been expected had the predicted radiogenic excess occurred. Interestingly, the estimates derived from the Japanese bomb survivors were based upon an average dose of only 0.24 Gy and on 70 lung cancer deaths among those receiving more than 0.5 Gy. Once again, our data are not consistent with the atom bomb surivor study where the total exposure time was only a fraction of a second.

The evaluation of excess risk was in large part made using general population rates for comparison and not the unexposed tuberculosis patients. Unfortunately, the direct comparison between exposed and unexposed groups lacked statistical power, inasmuch as the numbers of specific cancers were too small for site-, age-, time-, and dose-specific comparisons to yield meaningful results. Clearly, the general population was not an appropriate comparison for several noncancer deaths, such as those due to the underlying disease being treated (TB) and other respiratory diseases. For cancer deaths, however, the general population comparisons seem reasonable in most instances, especially since there is little evidence that TB per se is associated with increased cancer risks. Comparisons between exposed and unexposed for cancer deaths were nonetheless done cautiously because of peculiar increases in some cancers seen among unexposed males, *i.e.*, cancers of the buccal cavity, esophagus, large intestine, larynx, lung, and bladder. These excesses suggest that unexposed males differ from the general population and other TB patients in important factors that likely increase the risk of cancers previously linked to excessive alcohol consumption and cigarette smoking.

The results of our study should be interpreted in light of several methodological issues. Mortality does not present the full spectrum of radiation effects, since nonfatal diseases cannot be evaluated; the patients receiving pneumothorax treatment may have differed meaningfully from patients treated by other means; and the high force of mortality associated with TB and other lung diseases possibly could have obscured some radiation effects. We were also concerned that lung cancer might have been misclassified on death certificates and incorrectly recorded as TB. Although this may have occurred during the early years of treatment and active follow-up, it is unlikely that any such misclassification would have continued indefinitely. The absence of any variation of risk of lung cancer over time argues against, but does not completely discount, misclassification being a serious problem among long-term survivors. Several positive features of the study include the large numbers of patients studied, the completeness of the mortality follow-up, the long period of observation, the relatively accurate estimation of radiation doses to specific organs based on numbers of examinations and reconstructed exposure situations, and the availability of a comparison group of TB patients not subjected to frequent chest X-ray fluoroscopies.

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